IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Ziegler et al.
Application NO.: 10/084,676
FILED: 02/28/2002
FOR: ORAL PHARMACEUTICAL FORMS OF ADMINISTRATION WITH A DELAYED ACTION

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Ziegler, Iris, hereby declare as follows:

1. I am a citizen of Germany, residing at Im Dickenbruch 4, 52159 Roetgen, Germany;

2. I studied pharmacy at the University Munich (LMU) received a PhD degree in pharmaceutical technology in the year 1996.

3. Since 1996, I have been employed as a research pharmacist in the field of pharmaceutical technology and since 1997 up to now I have been working in this field for the company of Grünenthal GmbH at Aachen, Germany.

4. I am an inventor of the invention disclosed in the US Patent Application Serial No. 10/084,676.

5. The following tests were made under my supervision and control:

I Test according to US 5,914,129

Tablets of the following composition were prepared by direct compression.

composition	**per tablet**
Diclofenac-Na	50.0 mg
Tramadol- HCl	75.0 mg
Microcrystalline cellulose, (Avicel PH101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Crospovidone, (Kollidon CLM, BASF)	22.5 mg
Microcrystalline cellulose + lactose monohydrate, (Cellactose, Meggle)	256.0 mg
Lactose monohydrate	50.0 mg
Mg- stearate	1.4 mg
Total weight of a tablet	**529.9 mg**

For the production, the active substances, tramadol-HCl and diclofenac-Na, and the auxiliary substances mentioned above were screened through a 0.6 mm screen and then mixed for 10 minutes in a blender. The blend was compressed on a Korsch EK0 tablet press having a 15 x 6 mm die into 529.0 mg oblong shaped tablets.
The hardness of the tablets was approximately 100 N and disintegration time of the tablets was 5 minutes.

II Test according to US-patent application Serial No. 10/084,676

concerned a preparation of pellets containing an in situ formed compound of tramadol and diclofenac and having the composition set forth below:

75 g of tramadol hydrochloride, 50 g of sodium diclofenac and 37.5 g of microcrystalline cellulose (Avicel PH 101, FMC) and 37.5 g of colloidal microcrystalline cellulose (Avicel RC 591, FMC) were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then granulated with water in an amount sufficient for moistening. The sticky lumpy mass of granules was then extruded in a Nica extruder (type E140) with a 1.0 mm extrusion die. While the rods of extrudate were initially still extremely sticky, they changed in the course of the extrusion process to a very dry extrudate with insufficient plasticity for subsequent spheronization. The extrudate was moistened and granulated again. The resulting granules were extruded again in the Nica extruder and the moist extrudate was then converted to round pellets of uniform size in a Nica spheronizer (type S450). The pellets were dried in a drying cabinet at a temperature of approx. 50°C and fractionated into sieve fractions.

Composition of the pellets:

Tramadol hydrochloride	75.0 mg
Diclofenac sodium	50.0 mg
Lactose monohydrate	50.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC 591, FMC)	37.5 mg
	250 mg

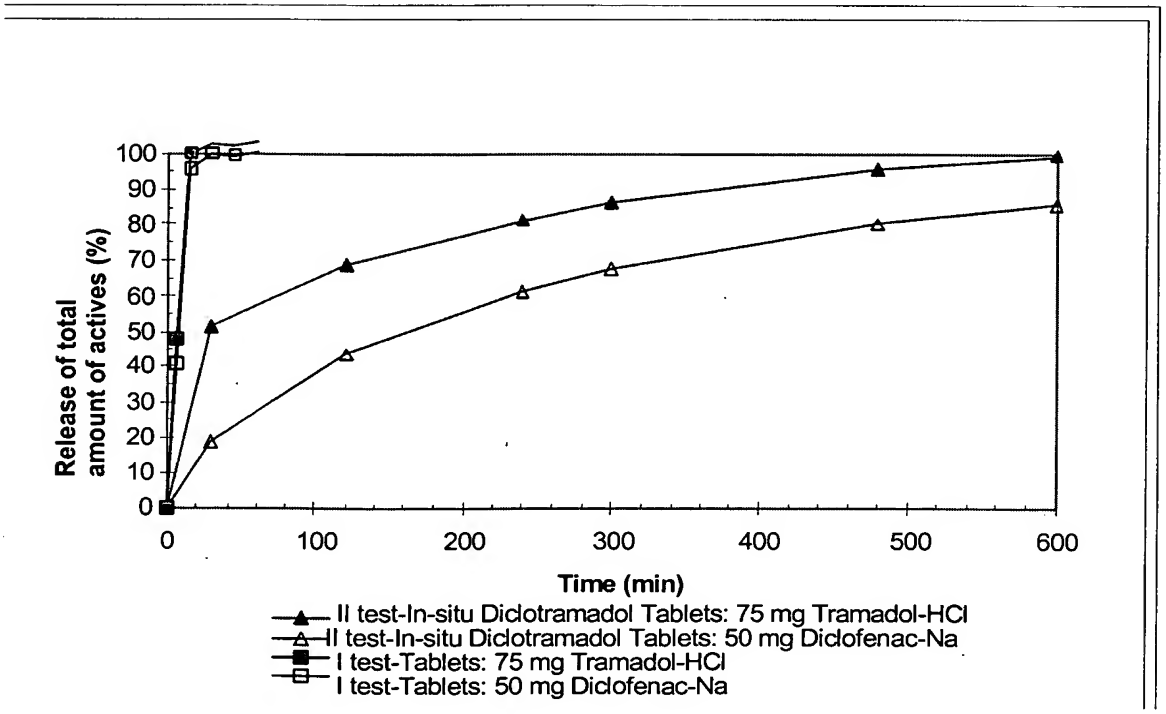
The desired sieve fraction of 0.63 – 0.8 µm of pellets were compressed into tablets with the following composition:

Composition	**per tablet**
in-situ prepared diclotramadol pellets	250.0 mg
Crospovidone, (Kollidon CLM, BASF)	22.5 mg
Microcrystalline cellulose + lactose monohydrate, (Cellactose, Meggle)	256.0 mg
Mg- stearate	1.4 mg
Total weight of a tablet	**529.9 mg**

The hardness of the tablets was approximately 60 - 80 N and disintegration time of the tablets into pellets was less than 2 minutes.

III Results:

The release profile of tramadol as well as of diclofenac was determined of tablets obtained according to Test I and Test II in 900 ml simulated intestinal fluid (pH 7.2) as described in US-patent application Serial No. 10/084,676 at a rotational speed of 50 rpm.



a.) The release of diclofenac as well as of tramadol from pellet-tablets containing the in situ compound was much slower than the release of the active compounds from tablets obtained by direct compression of tramadol-HCl and diclofenac-Na.

b.) The tablet obtained by direct compression showed a fast release of diclofenac as well as of tramadol within 15 minutes up to 100%.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that wilful false statements and the like, so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the patent application 10/084,676 or any patent issued thereon.

23 Sept 2005 — I. Ziegler

(Date) (Dr. Ziegler, Iris)